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Diastolic Dysfunction in Patients Undergoing Cardiac Surgery

A Pathophysiological Mechanism Underlying the Initiation of New-Onset Post-Operative Atrial Fibrillation

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Objectives Our goal was to investigate whether left ventricular (LV) diastolic dysfunction was an important pathophysiological mechanism underlying the initiation of new-onset post-operative atrial fibrillation (POAF).

Background Atrial fibrillation is a common complication after cardiac surgery. However, the precise mechanism underlying its development remains poorly understood. Pre-existing alterations of myocardial diastolic function may predispose patients to the development of POAF.

Methods Patients were residents of Olmsted County, Minnesota, who underwent complete LV diastolic function assessment before coronary artery bypass grafting and/or valve surgery between January 1, 2000, and December 31, 2005. All were in sinus rhythm and had no history of atrial fibrillation, a pacemaker, mitral stenosis, or congenital heart disease. POAF was defined as any episode of atrial fibrillation within 30 days after surgery.

Results POAF occurred in 135 of 351 patients (38.5%). Patients with POAF were older (mean age 72.5 ± 10.3 years vs. 63.1 ± 14.1 years; $p < 0.001$) and more likely to have abnormal diastolic function. The rate of POAF increased exponentially with diastolic function grade (DFG) severity ($p < 0.001$). By multivariate analysis, after adjusting for clinical and surgical risk factors, independent predictors of POAF were older age (odds ratio [OR]: 1.05; $p < 0.001$), higher body mass index (OR: 1.06; $p = 0.03$), and abnormal LV DFG (DFG 1, OR: 5.12 [$p = 0.006$]; DFG 2, OR: 9.87 [$p < 0.001$]; and DFG 3, OR: 28.52 [$p < 0.001$]).

Conclusions LV diastolic dysfunction is a powerful, independent predisposing substrate for the initiation of POAF. Evaluation may be useful during risk stratification of patients undergoing cardiac surgery. (J Am Coll Cardiol 2011;58: 953–61) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation (AF) occurs in a substantial subset of patients after cardiac surgery. It has been ascribed to various clinical risk factors closely linked to alterations of myocardial diastolic properties, including advanced age, hypertension, left ventricular (LV) hypertrophy, obesity, metabolic syndrome, LV dysfunction, and left atrial enlargement (1–5). New-onset post-operative atrial fibrillation (POAF) is a major cause of morbidity and mortality. It is associated with increased risk of stroke and death and constitutes a substantial use of healthcare resources, including increased duration of hospitalization and hospital costs (1,4,6–8).

Despite the documented clinical impact of POAF, there are no uniformly accepted treatments for its prevention, in part due to a lack of mechanistic understanding. Previous studies have focused on the determinants of POAF, but most factors are not modifiable, nor have researchers provided a clear physiological basis for pre-operative risk stratification or potential prophylactic treatment (1,4,9). Age, which is often associated with abnormal myocardial relaxation due to alterations in ventricular compliance (10–12), is the only risk factor most consistently identified as a major independent predictor for the development of POAF (1,3,9). The pathophysiological mechanisms of POAF therefore may be linked to pre-existing, age-related, and

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JACC Vol. 58, No. 9, 2011
August 23, 2011:953–61

Abbreviations and Acronyms

AF = atrial fibrillation
CABG = coronary artery bypass graft
CI = confidence interval
DFG = diastolic function grade
LV = left ventricular
OR = odds ratio
POAF = post-operative atrial fibrillation

degenerative structural and functional changes in the atrial and ventricular myocardium; these changes may contribute to the development of a proarrhythmic substrate that subsequently promotes the development of POAF. In this study, we sought to assess the hypothesis that impaired LV compliance is a principal culprit for the changing hemodynamic properties of the left atrium, predisposing patients to atrial arrhythmogenesis after cardiac surgery.

Methods

Study patients. The study was approved by the Mayo Clinic Institutional Review Board, and all patients gave written informed consent for participation in the study. It was conducted in Olmsted County, Minnesota, where comprehensive healthcare records with high-quality information have been maintained. Records covered all healthcare encounters and included clinical reports, echocardiographic reports, laboratory test results, pathology reports, and autopsy results. Complete medical records from consecutive Olmsted County patients were prospectively entered into a clinical database and retrospectively reviewed to investigate the relationship between diastolic dysfunction severity and the risk of developing new-onset POAF.

For the present investigation, eligible patients were residents of Olmsted County and could be of any age. The age of the study population was 66.7 ± 13.6 years, and 236 patients (67.2%) were men. All had pre-operative sinus rhythm and underwent isolated coronary artery bypass graft (CABG) and/or valvular repair or replacement (or some combination thereof), and survived the operation (n = 752). Our cohort did not include patients with congenital heart disease. We excluded patients with a pre-operative history of AF (n = 71), pacemaker (n = 37), Cox's maze or radiofrequency ablation procedure for atrial arrhythmias (n = 8), moderate or severe mitral stenosis (n = 16), and incomplete diastolic function assessment (n = 269). Standard care for these patients involved coordinated treatment between cardiologists and cardiac surgeons. All patients included in the study (n = 351) were Olmsted County residents, which facilitated prospective follow-up.

Echocardiographic data. All patients underwent a pre-operative, comprehensive transthoracic, 2-dimensional and Doppler echocardiographic evaluation with state-of-the-art technology within 3 months before surgery (median 6 days; interquartile range [IQR]: 1 to 25 days). All pre-operative echocardiograms were independently reviewed by 2 experienced echocardiographers in a blinded fashion. Disagreements about the diastolic function grade between the 2 independent physician reviews were resolved either by consensus or by arbitration by a third reviewer. Measurements of study variables were performed according to established methods (13–15). Diastolic parameters were integrated to form a global diastolic function score (grades 0–3) (13–17).

- Grade 0: Normal LV filling pressure; mitral E/A ratio of 0.75 to 1.5, mitral deceleration time 160 to 240 ms, e' ≥8, E/e' <8, pulmonary venous systolic forward flow velocity > diastolic, pulmonary venous atrial reversal duration shorter than mitral A flow duration, and left atrial volume index <34 ml/m^2.
- Grade 1: Normal to mildly elevated LV filling pressure or impaired LV relaxation; mitral E/A ratio of <0.75, mitral deceleration time >240 ms, e' <8, E/e' ≤8, pulmonary venous systolic forward flow velocity ≥diastolic, pulmonary venous atrial reversal duration shorter than mitral A flow duration, and left atrial volume index ≥34 ml/m^2.
- Grade 2: Moderately elevated LV filling pressure or pseudonormal LV diastolic filling; mitral E/A 0.75 to 1.5 with a decrease of ≥0.5 with Valsalva maneuver, mitral deceleration time 160 to 240 ms, e' <8, E/e' 9 to 12, pulmonary venous systolic forward flow velocity < diastolic, pulmonary venous atrial reversal duration longer than mitral A flow duration (by ≥30 ms), and left atrial volume index ≥34 ml/m^2.
- Grade 3: Severely increased LV filling pressure or restrictive LV diastolic filling; mitral E/A >1.5 with a decrease of ≥0.5 (reversible) or <0.5 (fixed) with Valsalva maneuver, mitral deceleration time <160 ms, e' <8, E/e' ≥13, pulmonary venous systolic forward flow velocity < diastolic, pulmonary venous atrial reversal duration longer than mitral A flow duration (by ≥30 ms), and left atrial volume index ≥34 ml/m^2.

Electrocardiography. All patients were monitored for the occurrence of POAF with continuous electrocardiographic telemetry until the day of hospital dismissal. A standard, 12-lead electrocardiogram was recorded on the day of dismissal for each patient. POAF was based on documentation of AF episodes by continuous telemetry throughout hospitalization or electrocardiogram during follow-up within 30 days after cardiac surgery.

Angiography. Coronary angiography results were obtained from clinical reports composed by experienced angiographers at the time of cardiac catheterization. The degree of coronary artery stenosis was visually estimated as a percentage of the normal segment preceding the stenosis. Clinically significant coronary stenoses were defined as ≥70% narrowing of the luminal diameter of ≥1 major epicardial arteries or a ≥50% left main artery stenosis. Patients with left main coronary artery stenosis were considered to have 2-vessel disease if there was right coronary dominance and 3-vessel disease if there was left dominance.

Clinical predictors. On the basis of previous reports (1–5,8,9,18), the covariates analyzed included pre-operative

echocardiographic data, angiographic data, patient demographic data, coexisting medical conditions, pre-operative cardiac medication use, and surgical factors.

Follow-up and outcome assessment. Patient records were reviewed to ascertain the presence or absence of POAF within 30 days after surgery. The 30-day clinical follow-up was obtained by review of medical records, mailed surveys, and telephone interviews. Patients who underwent a repeat operation within 30 days of their indexed cardiac surgical procedure were censored at time of repeat surgery.

Statistical analysis. Data are presented as proportions (%) for categorical variables and as mean ± SD or median (IQR) when appropriate for continuous variables. For skewed variables, the median (range) is reported. Univariate association of variables with the outcome of POAF within 30 days was assessed using multivariable logistic regression. For each variable, the odds ratio (OR), 95% confidence interval (CI), and p value are provided.

Exploratory data analyses were conducted using univariate summaries to examine distributions of key variables. Variables significantly associated with POAF after univariate analysis ($p < 0.05$) and those that were established risk factors were entered in a multivariable logistic regression model to identify the independent predictors of POAF. The performance of the risk model was determined by using C statistics, equivalent to the area under the receiver operating characteristic curve. A C statistic of 0.5 indicates that the model predictions are no better than chance (i.e., equal numbers of true and false positives), >0.7 indicates acceptable predictive ability, and 1 implies a model with perfect predictive ability.

Post-operative complications and length of hospitalization were compared for patients with and without POAF using the chi-square test and Wilcoxon rank sum tests, respectively. The p value of 0.05 was selected as the threshold of statistical significance. Statistical analyses were performed using SAS software version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics. Table 1 shows criteria for gradation of diastolic function. The baseline characteristics of the patients are summarized in Table 2 (data are stratified according to occurrence of new-onset POAF and show respective univariate p values). Overall, patients with POAF were more likely to be older (OR: 1.06; 95% CI: 1.04 to 1.08; $p < 0.001$) and had baseline renal insufficiency (OR: 2.02; 95% CI: 1.05 to 3.92; $p = 0.04$) compared with those who did not have POAF. The extent of obstructive coronary artery disease and pre-operative use of beta-blockers, antiarrhythmic agents, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, statins, or diuretics did not differ significantly between the 2 groups.

Incidence and clinical course of new-onset POAF. The overall incidence of new-onset POAF was 38.5% (n = 135) and peaked at a median of 2 days (range 0 to 28 days), lasting a median of 2 days (range 0.04 to 18 days). Sinus rhythm was restored in 99.3% of patients before hospital dismissal. Thirty-seven patients (27.4%) spontaneously converted to sinus rhythm while receiving rate-controlling agents, 71 patients (52.6%) received class III antiarrhythmic medications, 5 patients (3.7%) underwent electrical cardioversion, and 21 patients (15.6%) were treated with both forms of cardioversion. The last patient who developed AF 4 days after hospital dismissal was managed with rate control and anticoagulation and remained in persistent AF at 30-day follow-up.

Surgical data are presented in Table 3. Isolated CABG surgery was performed in 160 patients (45.6%), aortic valve surgery in 128 (36.5%), mitral valve surgery in 70 (19.9%), tricuspid valve surgery in 5 (1.4%), pulmonic valve surgery in 1 (0.3%), and combined CABG and valve procedures in 76 (21.7%). By univariate analysis, surgical factors predictive of POAF were mitral valve procedures (OR: 2.42; 95% CI: 1.43 to 4.15; $p = 0.001$) and combined CABG and valve procedures (OR: 2.57; 95% CI: 1.47 to 4.49; $p < 0.001$). There was a trend toward higher rates of POAF in patients who had multivalvular surgery (OR: 8.31; 95% CI: 0.91 to 76.2; $p = 0.06$). No other surgical variable was shown to be significantly associated with POAF.

The rate of POAF differed according to the complexity of the surgical procedure performed (Fig. 1). Although the

Table 1 Doppler Criteria for Classification of Diastolic Function and Estimation of LV Filling Pressure

Criteria	Grade 0 (Normal Diastolic Function)	Grade 1 (Impaired Relaxation)	Grade 2 (Pseudonormal)	Grade 3 (Reversible/Fixed Restrictive)
Mitral inflow	E/A 0.75–1.5, DT 160–240 ms	E/A <0.75, DT >240 ms	E/A 0.75–1.5, DT 160–240 ms	E/A >1.5, DT <160 ms
Mitral inflow at peak Valsalva maneuver	ΔE/A <0.5	ΔE/A <0.5	ΔE/A ≥ 0.5	ΔE/A ≥ 0.5/<0.5
Septal e'	≥8	<8	<8	<8
TDI of mitral annular motion	E/e' <8	E/e' ≤8	E/e' ≥ 9–12	E/e' ≥13
Pulmonary venous flow	S > D, ARdur < Adur	S ≥ D, ARdur < Adur	S < D, or ARdur-Adur ≥30 ms	S < D, or ARdur-Adur ≥30 ms
LA volume	<34 ml/m^2	≥34 ml/m^2	≥34 ml/m^2	≥34 ml/m^2
LV compliance	Normal	Normal to ↓	↓ ↓	↓ ↓ ↓
LV filling pressure	Normal	Normal to ↑	↑ ↑	↑ ↑ ↑

A = mitral A-wave velocity at atrial contraction; Adur = mitral A-wave duration; ARdur = pulmonary vein atrial reversal flow duration; D = pulmonary vein diastolic forward flow; DT = mitral E-wave deceleration time; e' = velocity of mitral annulus early diastolic motion; E = peak mitral early filling velocity; LA = left atrial; LV = left ventricular; S = pulmonary vein systolic forward flow; TDI = tissue Doppler imaging.

JACC Vol. 58, No. 9, 2011
August 23, 2011:953–61

Table 2 Baseline Characteristics of the Study Population According to the Occurrence of New-Onset POAF

Characteristic	No POAF (n = 216)	POAF (n = 135)	OR	95% CI	p Value
Age (yrs)	63.1 ± 14.1	72.5 ± 10.3	1.06	1.04–1.08	<0.001
Men	149 (69.0)	87 (64.4)	0.80	0.51–1.27	0.35
Body surface area (m^2)	1.94 ± 0.23	1.96 ± 0.25	1.28	0.51–3.22	0.60
Body mass index (kg/m^2)	28.5 ± 5.0	29.3 ± 5.4	1.03	0.99–1.07	0.20
Heart rate (beats/min)	69.2 ± 12.9	69.1 ± 12.8	1.00	0.98–1.02	0.93
Systolic blood pressure (mm Hg)	130.5 ± 24.5	133.3 ± 25.2	1.00	0.99–1.01	0.90
Pulse pressure (mm Hg)	63.3 ± 22.3	66.4 ± 20.8	1.01	0.99–1.02	0.20
MAP (mm Hg)	90.7 ± 13.2	89.0 ± 15.8	0.99	0.98–1.01	0.27
Hypertension	153 (70.8)	107 (79.3)	1.57	0.95–2.65	0.08
Diabetes mellitus	57 (26.4)	34 (25.2)	0.96	0.58–1.57	0.86
Dyslipidemia	147 (68.1)	101 (74.8)	1.38	0.85–2.24	0.19
Peripheral vascular disease	32 (14.8)	25 (18.5)	1.31	0.73–2.31	0.37
Previous myocardial infarction	40 (18.5)	28 (20.7)	1.13	0.66–1.95	0.65
Creatinine >1.5 mg/dl	19 (8.8)	22 (16.3)	2.02	1.05–3.92	0.04
Smoking	143 (66.2)	84 (62.2)	0.85	0.54–1.33	0.47
Chronic lung disease	35 (16.2)	23 (17.0)	1.09	0.61–1.95	0.76
Pre-operative medication					
Beta-blocker	136 (63.0)	89 (65.9)	1.14	0.72–1.79	0.57
Calcium channel blocker	45 (20.8)	29 (21.5)	1.04	0.60–1.75	0.88
Antiarrhythmic agent	1 (0.5)	2 (1.5)	3.23	0.31–69.90	0.32
ACE inhibitor	90 (41.7)	62 (45.9)	1.19	0.77–1.83	0.43
Angiotensin-receptor blocker	18 (8.3)	17 (12.6)	1.60	0.79–3.24	0.18
Diuretics	73 (33.8)	54 (40.0)	1.31	0.84–2.04	0.24
Thyroxin	27 (12.5)	15 (11.1)	0.88	0.44–1.69	0.69
Statin	114 (52.8)	76 (56.3)	1.14	0.74–1.76	0.55
Digoxin	6 (2.8)	6 (4.4)	1.63	0.50–5.31	0.41
Aspirin	165 (76.4)	107 (79.3)	1.18	0.70–2.01	0.53
Angiographic data (n = 323)					
Diseased vessels	1.73 ± 1.2	1.57 ± 1.2	0.98	0.72–1.35	0.31
LM stenosis ≥50%	33 (17.2)	20 (15.3)	0.65	0.23–2.05	0.65
LAD stenosis ≥70%	111 (57.8)	69 (52.7)	0.92	0.35–1.28	0.36
LCx stenosis ≥70%	81 (42.2)	56 (42.7)	0.56	0.28–1.10	0.92
RCA stenosis ≥70%	99 (51.6)	60 (45.8)	0.90	0.48–1.71	0.31

Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; BMI = body mass index; BSA = body surface area; CI = confidence interval; LAD = left anterior descending; LCx = left circumflex; LM = left main; MAP = mean arterial pressure; MI = myocardial infarction; OR = odds ratio; POAF = post-operative atrial fibrillation; PVD peripheral vascular disease; RCA = right coronary artery.

incidence of POAF in the isolated CABG group (52 of 160 [32.5%]) and in the single-valve group (37 of 110 [33.6%]) did not differ significantly (p = 0.85), patients who underwent more complex procedures, such as combined CABG and valvular surgery (42 of 76 [55.3%]) and isolated multiple-valve surgery (4 of 5 [80.0%]), had significantly higher rates of POAF compared with those who underwent isolated CABG (p < 0.001 and p = 0.03, respectively).

Table 3 Univariable Surgical Predictors of POAF

Procedure	No POAF (n = 216)	POAF (n = 135)	OR	95% CI	p Value
Isolated CABG	108 (50.0)	52 (38.5)	0.73	0.47–1.12	0.15
Mitral valve procedures	31 (14.5)	39 (28.9)	2.42	1.43–4.15	0.001
Aortic valve procedures	77 (35.7)	51 (37.8)	1.10	0.70–1.71	0.68
Isolated single valves	73 (33.8)	37 (27.4)	1.07	0.64–1.79	0.81
Isolated multiple valves	1 (0.5)	4 (3.0)	8.31	0.91–76.2	0.06
Combined CABG and valve	34 (15.7)	42 (31.1)	2.57	1.47–4.49	<0.001
Perfusion time (min)	77.3 ± 44.8	84.1 ± 37.8	1.00	1.00–1.01	0.15
Cross-clamp time (min)	50.3 ± 27.5	55.8 ± 27.7	1.01	1.00–1.02	0.08
IABP intraoperatively	11 (5.1)	9 (6.7)	1.32	0.53–3.29	0.54
Ventilation time (h)	17.69 ± 41.8	30.34 ± 67.0	1.00	1.00–1.01	0.06

Values are n (%) or mean ± SD.

CABG = coronary artery bypass graft surgery; IABP = intra-aortic balloon pump; other abbreviations as in Table 2.

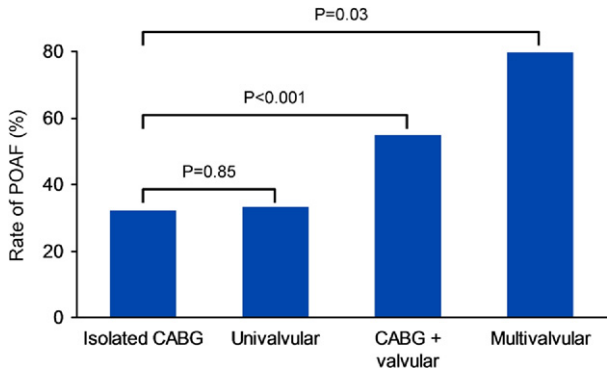

Figure 1 **Incidence of POAF According to Surgical Procedure Performed**

The incidence of post-operative atrial fibrillation (POAF) increased significantly according to the complexity of the surgical procedure performed.

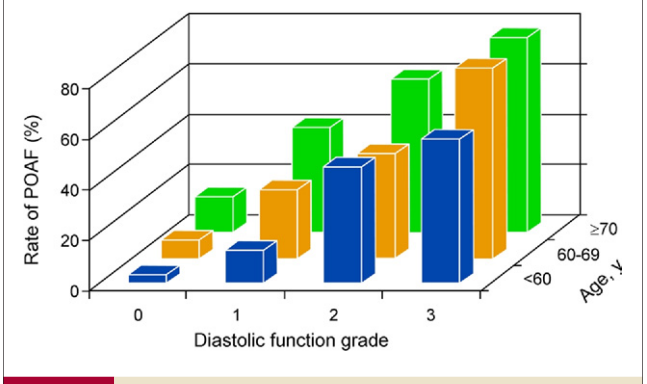

Figure 2 **Incidence of POAF as a Function of Age and Diastolic Function**

The rate of post-operative atrial fibrillation (POAF) increased significantly across diastolic function grades (stratified by age). Grade 1 versus 0, p = 0.006; grade 2 versus 0, <0.001; grade 3 versus 0, <0.001.

Role of diastolic function in development of new-onset POAF. Pre-operative echocardiographic hemodynamic parameters are listed in Table 4. There was an exponential increase in the rate of POAF across diastolic function grades (DFGs) (Fig. 2). Overall, the rate of POAF increased significantly across DFGs (unadjusted): grade 1 versus 0, <0.001; grade 2 versus 0, <0.001; grade 3 versus 0, <0.001. Only 5.1% (4 of 79) of patients with normal LV diastolic function (grade 0) had POAF compared with 34.6% (36 of 104) who had grade 1 LV diastolic dysfunction, 58.2% (78 of 134) with grade 2 LV diastolic dysfunction, and 70.8% (17 of 24) with grade 3 LV diastolic dysfunction ($p < 0.001$). However, patients younger than age 60 years with lower grades of LV diastolic dysfunction (grades <2) were a lower-risk group (<15% risk of developing POAF). A small proportion of the total population (n = 55 [15.7%]) had moderate or more severe mitral regurgitation. Among patients who had LV end-diastolic pressure measured invasively (n = 216), DFG was significantly correlated with LV end-diastolic pressure ($r = 0.62$; $p < 0.001$), even in the presence of mitral regurgitation.

According to univariate analysis, patients with abnormal DFG were more likely than those with normal DFG to have new-onset POAF (grade 1, OR: 9.9; 95% CI: 3.41 to 29.8; $p < 0.001$; grade 2, OR: 22.2; 95% CI: 7.69 to 63.8; $p < 0.001$; and grade 3, OR: 45.5; 95% CI: 12.0 to 173.0; $p < 0.001$). Patients who developed POAF had a significantly higher E/e' ratio (17.3 ± 8.2 vs. 14.4 ± 7.8; $p = 0.005$) and left atrial volume index (42.5 ± 15.0 ml/m^2 vs. 34.2 ± 12.8 ml/m^2; $p < 0.001$) compared with those who did not. An E/e' of ≥10 was associated with a 4-fold higher risk of POAF (OR: 4.01; 95% CI: 1.84 to 10.3; $p < 0.001$),

Table 4 **Univariable Echocardiographic Predictors of POAF**

Factor	No POAF (n = 216)	POAF (n = 135)	OR	95% CI	p Value
Diastolic function grade 0	75 (34.7)	4 (3.0)	1.0	–	–
Diastolic function grade 1	68 (31.5)	36 (26.7)	9.9	3.41–29.8	<0.001
Diastolic function grade 2	66 (30.6)	78 (57.8)	22.2	7.69–63.8	<0.001
Diastolic function grade 3	7 (3.2)	17 (12.6)	45.5	12.00–173.0	<0.001
e' (cm/s)	6.5 ± 2.22	5.9 ± 1.7	0.87	0.76–0.99	0.03
E/e'	14.4 ± 7.8	17.3 ± 8.2	1.04	1.01–1.08	0.005
E/A	1.17 ± 0.62	1.25 ± 0.74	1.21	0.88–1.68	0.24
Mitral E-wave DT (ms)	218.0 ± 49	215.3 ± 56	1.00	0.99–1.00	0.64
PV peak systolic velocity (cm/s)	0.57 ± 0.17	0.58 ± 0.16	1.65	0.38–7.12	0.50
PV peak diastolic velocity (cm/s)	0.48 ± 0.17	0.51 ± 0.20	2.87	0.77–10.8	0.11
PVaR velocity (cm/s)	0.31 ± 0.22	0.30 ± 0.06	0.88	0.12–3.69	0.85
LAVI (ml/m^2)	34.2 ± 12.8	42.5 ± 15.0	1.04	1.03–1.06	<0.001
LAVI ≥34 ml/m^2	78 (41.3)	85 (70.3)	3.36	2.08–5.51	<0.001
LV mass index (g/m^2)	115.9 ± 37.8	122.2 ± 39.2	1.00	0.99–1.01	0.17
LVEF (%)	55.4 ± 13.2	56.1 ± 13.7	1.00	0.99–1.02	0.60
Mitral regurgitation (>moderate)	30 (13.9)	29 (21.5)	1.69	0.96–2.96	0.07

Values are n (%) or mean ± SD.
LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; other abbreviations as in Tables 1 and 2.

JACC Vol. 58, No. 9, 2011
August 23, 2011:953–61

Table 5 Multivariate Logistic Regression Model for Predicting New-Onset POAF After Cardiac Surgery

Covariates	OR	95% CI	p Value
Age (yrs)	1.05	1.02–1.08	<0.001
BMI (kg/m^2)	1.06	1.01–1.11	0.03
Hypertension	1.03	0.55–1.95	0.92
Mitral regurgitation (>moderate)	1.85	0.83–4.12	0.13
Diastolic function grade 1	5.12	1.60–16.38	0.006
Diastolic function grade 2	9.87	3.23–30.13	<0.001
Diastolic function grade 3	28.52	7.11–114.44	<0.001
Univalvular surgery	0.90	0.46–1.73	0.75
Multivalvular surgery	4.49	0.46–43.60	0.20
CABG + valvular surgery	1.42	0.69–2.91	0.34
Perfusion time	1.00	0.99–1.01	0.89

n = 351; chi-square test = 102.09; area under the receiver operating characteristic curve = 0.78. BMI = body mass index; other abbreviations as in Tables 2 and 3.

with a sensitivity of 93% and a specificity of 23%. A left atrial volume index of ≥34 ml/m^2 was associated with a 3-fold higher risk of POAF (OR: 3.36; 95% CI: 2.08 to 5.51; p < 0.001), with a sensitivity of 70% and a specificity of 59%. The optimal diastolic grade cut-point to identify patients with POAF was DFG 2 (sensitivity 70.3%; specificity 67.0%). The area under the receiver operating characteristic curve was 0.734.

Multivariate logistic regression model for predicting new-onset POAF. In multivariate logistic regression analysis (Table 5), after adjusting for surgical and clinical risk factors, including more than moderate mitral regurgitation, the independent predictors of new-onset POAF were older age (OR: 1.05; 95% CI: 1.02 to 1.08; p < 0.001), higher body mass index (OR: 1.06; 95% CI: 1.01 to 1.11; p = 0.03), and LV diastolic dysfunction. Grade 1 diastolic dysfunction (impaired relaxation) had an OR of 5.12 (95% CI: 1.60 to 16.38; p = 0.006), grade 2 diastolic dysfunction (pseudonormal) had an OR of 9.87 (95% CI: 3.23 to 30.13; p < 0.001), and grade 3 diastolic dysfunction reversible or fixed restrictive) had an OR of 28.52 (95% CI: 7.11 to 114.44; p < 0.001) for predicting the risk of developing POAF when compared with normal diastolic function (grade 0). No procedure-related variables independently predicted POAF. The C statistic was calculated and included the independent predictors of POAF from the logistic regression analysis. The area under the receiver operating characteristic curve for the multivariate prediction model was 0.78, confirming the predictive power of the regression analysis.

In a subanalysis, we assessed the usefulness of left atrial volume index with and without DFG included in the model. In the absence of DFG, left atrial volume index was an independent predictor of POAF (OR: 1.04; 95% CI: 1.01 to 1.06; p = 0.002). However, this relationship was attenuated after adjustment for pre-operative grade of LV diastolic dysfunction (OR: 1.02; 95% CI: 1.00 to 1.05; p = 0.07). The addition of left atrial volume index did not affect the predictive power of DFG to estimate the risk of POAF.

Figure 3 displays the results of the incremental models for the prediction of new-onset POAF. The C statistic was calculated to evaluate the incremental value of left atrial volume index and diastolic dysfunction for the prediction of POAF above surgical and clinical risk factors alone and combined. The C statistic increased from 0.60 and 0.73 for surgical and clinical risk factors alone, respectively, to 0.74 for combined clinical and surgical risk factors. When left atrial volume index was added, the C statistics increased from 0.74 to 0.76, whereas the addition of diastolic dysfunction improved prediction of POAF from 0.74 to 0.78. The addition of both diastolic dysfunction and left atrial volume index improved the model even further by increasing the C statistic value from 0.74 to 0.80.

Impact of POAF on clinical outcomes. During the 30-day follow-up, post-operative complications, including acute renal failure, new-onset renal failure requiring hemodialysis, stroke, and death, were more common in patients with POAF (n = 28 [21%]) compared with those without POAF (n = 18 [9.7%]) (p = 0.006). Patients with POAF had significantly higher rates of post-operative acute renal failure (creatinine >1.5 mg/dl) (8.9% vs. 1.9%; p = 0.002) and new-onset renal failure requiring hemodialysis (5.9% vs. 0.9%; p = 0.006) compared with those without POAF. Patients with POAF had a correspondingly longer duration of hospitalization than patients without POAF (median 8 vs. 6 days; IQR: 6 to 11 days vs. 5 to 8 days; p < 0.001). The rate of new stroke and 30-day mortality did not differ between the 2 groups (1.9% vs. 3.0%; p = 0.50) and 8 (3.7%) versus 4 (3.0%) (p = 0.71), respectively.

Discussion

Main findings. This study is, to our knowledge, the first report to demonstrate that patients with LV diastolic dysfunction are a population at high risk for the develop-

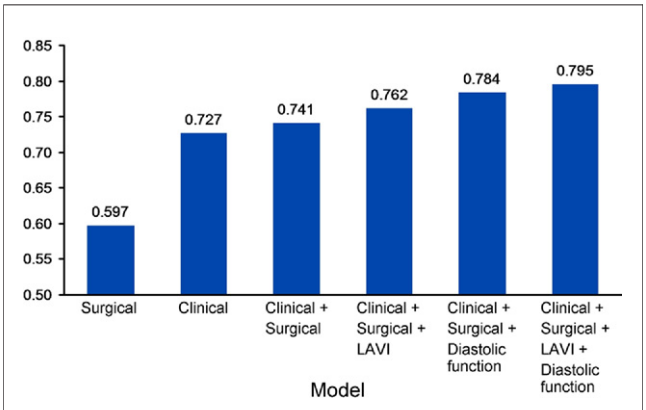

Figure 3 Model C Statistics

Bar graph illustrating the incremental predictive value of 6 different models for the development of new-onset post-operative atrial fibrillation (POAF). A model including the addition of diastolic dysfunction to surgical and clinical risk factors and left atrial volume index yielded the best prediction of new-onset POAF. C statistic value improved from 0.74 to 0.80.

ment of new-onset AF after cardiac surgery. In our cohort, diastolic dysfunction was a powerful independent predictor of POAF. The rate of POAF increased exponentially across LV DFGs. This finding may help clinicians stratify patients undergoing cardiac surgery for risk of POAF and may be used to plan preventive strategies for selected high-risk individuals. Our data indicate that elevated LV filling pressure due to abnormal LV diastolic function is a potential physiological substrate for the initiation of POAF. This study, therefore, establishes diastolic dysfunction as an important predisposing factor for the initiation of new-onset POAF after the additional physiological stress of cardiac surgery. Interestingly, although LA volume independently predicted new-onset POAF in the absence of DFG, this relationship was attenuated on adjustment for DFG without affecting the predictive power of DFG to estimate the risk of POAF. This finding suggests that in the absence of diastolic function assessment, LA volume, which reflects the cumulative effects of LV filling pressures over time, may be an acceptable surrogate of POAF risk assessment. Our study was performed in a large, community-based population of patients with and without impaired ejection fraction, which adds statistical strength and generalizability to this observation. Pre-operative, noninvasive diastolic function assessment allows patients to be stratified regarding the risk of POAF development and gives credence to pre-operative management of LV filling pressure as a potential method of reducing risk of POAF.

Incidence and clinical course of POAF. In this report, the estimated incidence of POAF was 38.5%, which is in accordance with the literature (4,6,9). The incidence of new-onset POAF peaked at a median of 2 days (range 0 to 28 days) after cardiac surgery, which corresponded to time to peak inflammation and volume overload due to mobilization of fluid that has "third-spaced" post-operatively (19,20). POAF lasted a median of 2 days (range 0.04 to 18 days) and extended the patients' duration of hospitalization by an average of 2 days, suggesting that POAF may be an influential contributor to increased hospital costs in patients undergoing cardiac surgery. In keeping with results of previous reports (6,9), complex cardiac surgical procedures were associated with a higher frequency of POAF. This finding suggests that the complexity of the surgical procedure may amplify the risk associated with cardiac surgery itself; changes mediated by stress on the atria in the context of impaired LV compliance can increase vulnerability to development of POAF.

Comparison with previous studies. Several prior studies have analyzed predictors of POAF. However, many were subject to referral bias (1,4–6), included patients with a history of AF (3–5), or confined their analysis to patients undergoing isolated CABG surgery (1,18,21), which limited a wider extrapolation of their findings. The risk factors identified in our population-based series predict the occurrence of POAF more accurately than those derived from more highly selected patient groups. Advanced age has been the only consistent, yet immutable, independent predictor of POAF (3,5,9,21). This finding is probably due to the high frequency of age-related structural changes such as degeneration of large-vessel elastin, increase in afterload, altered filling dynamics, atrial dilation, fibrosis, and electrical heterogeneity (10–12,22).

In keeping with results of prior studies (1,4,18), the occurrence of POAF was significantly associated with other post-operative complications. Diastolic dysfunction was likely a predisposing common denominator underlying these endpoints. Indeed, similar to the study of Albahrani et al. (20), our study reported a significant difference in the incidence of new-onset acute renal dysfunction and renal dysfunction requiring dialysis in patients with POAF, suggesting that volume overload, in the background of impaired diastolic distensibility, likely elevates atrial pressure and potentiates the development of POAF.

Pathophysiological mechanism of new-onset POAF: role of diastolic dysfunction. Aging is associated with an increase in fibrosis (22,23), which results in progressive remodeling and increased stiffness of the atrial and ventricular myocardium. Atrial interstitial fibrosis increases with age in animal models and in humans; it has been observed particularly in patients with AF (24–26). This increase in atrial fibrosis corresponds to an increase in conduction heterogeneity and AF vulnerability (27,28). Through these studies, it has been shown that atrial fibrosis and impaired LV compliance, especially when superimposed by the acute stress of surgical intervention (29), create a profibrillatory environment that is manifested clinically as POAF.

Diastolic dysfunction is associated with an increasing stretch in pulmonary veins due to increased left atrial pressure (30). As previously reported by Chang et al. (31), the stretch-induced increase in the arrhythmogenic activity of the pulmonary veins due to impaired diastolic distensibility, as extrapolated from the present study, may have an important role in the pathophysiology of POAF.

Clinical implications. To date, prophylactic therapies for POAF are largely empirical. We have identified a pathophysiological mechanism underlying the development of POAF, which may provide a target for development of novel preventive therapies. The present study suggests that a pre-existing condition (e.g., reduced LV compliance) and a trigger (e.g., cardiac surgery) are necessary for the development of POAF. We have shown that irrespective of age, the more severe the DFG, the higher the risk of POAF. This finding suggests that POAF may be preventable by optimizing pre-operative management of LV filling hemodynamics, particularly for patients with DFG 2 or higher.

Pre-operative 2-dimensional and Doppler echocardiography findings showing impairment of diastolic filling should be investigated. Specifically tailored strategies that aim to decrease LV diastolic filling pressure pre-operatively may be a potential strategy of prophylaxis against POAF in high-risk patients undergoing cardiac surgery. Our findings suggest that aggressive preventative measures should be applied to high-risk patients undergoing cardiac surgery. In

modern clinical practice, altering the degree of LV diastolic dysfunction pre-operatively to influence the risk of POAF in the short term is currently not possible. Therefore, a more practical approach might be to target individuals at the highest risk (≥grade 2 diastolic dysfunction) for prophylaxis with antifibrillatory therapy before cardiac surgery.

Study strengths and limitations. The major strengths of this study are its large, population-based cohort of patients that included men and women from a broad age range and the detailed, prospective collection of data that included information about numerous potential confounders. Knowledge of independent physiological predictors for POAF and associated complications may more accurately define risk and aggressively optimize pre-operative physiology.

There are several limitations to the interpretation of our data. In the present study, a small proportion of the total population had clinically significant mitral regurgitation, which potentially could have affected results. However, among patients who had LV end-diastolic pressure measured invasively, DFG was significantly correlated with LV end-diastolic pressure, even in the presence of mitral regurgitation. Additionally, when patients with significant mitral regurgitation were excluded from the analysis, results did not change. Moreover, in multivariate analysis, the impact of mitral regurgitation on the occurrence of POAF was insignificant.

Our study investigated AF that occurred within 30 days after surgery. POAF cases, especially those with paroxysmal AF, likely were missed if they occurred outside of the hospital setting. As a result, we may have underestimated the incidence of POAF, which should bias the results in favor of the null hypothesis and against the significant association between diastolic dysfunction and new-onset POAF in this study. However, we studied a unique, community-based sample, drawn from a local population that receives most of its medical care at the Mayo Clinic. All patients were surveyed and all clinically available means were used to capture all occurrences of POAF. In addition, our findings were consistent with those of many studies and showed that most POAF episodes occurred in the first 3 days after cardiac surgery (1,5). Another limitation of this study is the lack of specific data for systemic inflammation, an important consideration in the post-operative state. However, in our study, the incidence of POAF peaked on the second post-operative day, which corresponds to time to peak inflammation after cardiac surgery (19).

Conclusions

Diastolic dysfunction is a powerful predisposing substrate for the initiation of POAF after cardiac surgery. Pre-operative assessment of diastolic function allows identification of high-risk patients who might benefit from prophylactic treatment and may provide useful prognostic information for individual patients. Further studies are needed to show whether reduction of LV filling pressure before cardiac surgery is correlated with a consequent reduction in the risk of POAF.

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